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TITLE: Integrating Radiomics and Genomics to Improve the Clinical Assessment of Pancreatic Cysts and Early Detection of Pancreatic Cancer

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14. ABSTRACT With the rapid utilization and ongoing advancements in cross-sectional abdominal imaging, the detection of pancreatic cysts has become increasingly frequent. It is reported pancreatic cysts are identified in 1.2-2.6% of abdominal computed tomography (CT) scans. Many of these cysts, including serous cystadenomas (SCA) and pseudocysts, are benign and can be monitored clinically. In contrast, mucinous cysts, which include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs), have the potential to progress to pancreatic adenocarcinoma (PDAC). Currently, a multidisciplinary approach is recommended in the assessment of pancreatic cysts. This includes clinical and radiographic evaluation, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), cytology, cyst fluid analysis (e.g., viscosity) and tumor markers (e.g., carcinoembryonic antigen (CEA)). Despite a combination of methodologies, the distinction between mucinous cysts from other pancreatic cysts can be difficult. Moreover, the detection of PDAC within a pancreatic cyst can be even more challenging. Thus, there is a dire need for biomarker assays that can accurately differentiate mucinous from non-mucinous pancreatic cysts and the presence versus absence of advanced neoplasia within a pancreatic cyst. This proposal represents the formation of a multi-institutional team of investigators to evaluate promising radiomic and genomic biomarkers to improve the initial evaluation and follow-up for patients with pancreatic cysts.

15. SUBJECT TERMS None listed.

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1. **INTRODUCTION:** PDAC is one of the most lethal cancers in the United States (US) and is associated with a dismal 5-year survival rate of 9%. Considering PDAC is a relatively uncommon cancer, screening of the general population is not feasible nor recommended by the US Preventive Services Task Force. Alternatively, the evaluation of high-risk individuals, such as patients with mucinous pancreatic cysts, is recommended. Mucinous cysts of the pancreas include intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) and represent precursors to PDAC. Importantly, mucinous cysts have a high prevalence in the US. Based on current US census data, it is estimated that >6 million Americans harbor a mucinous cyst, and, within this large subset of the US population, the vast majority are over the age of 40 years. In addition, discriminating between mucinous cysts and other pancreatic cysts, such as serous cystadenomas (SCAs) and pseudocysts, which often follow a benign clinical course, can be challenging. Moreover, most mucinous cysts are indolent and only a minority will undergo malignant transformation. Consequently, several medical societies have established guidelines for the diagnosis, evaluation, and treatment of patients with pancreatic cysts. These guidelines rely on a multidisciplinary approach to include clinical presentation, abdominal computed tomography (CT) or magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), and pancreatic cyst fluid analysis for CEA analysis and cytologic evaluation. However, these diagnostic modalities suffer from poor performance in identifying mucinous cysts and detecting advanced neoplasia (high-grade dysplasia and early-stage PDAC) within a mucinous cyst. As surgical intervention remains the preferred treatment option for mucinous cysts, patients and their physicians must consider the operative mortality and morbidity of these procedures, which range from 2% to 4% and 40% to 50%, respectively, when making management decisions. Hence, a diagnosis of a pancreatic cyst results in significant anxiety for both the patient and his or her physician. We propose to integrate radiomics and genomics to characterize the biology of pancreatic cysts and improve clinical management.

   Please note that this report focuses on the progress made at MD Anderson Cancer Center, where our role on this DOD grant was to perform the radiomic analyses. Please see the reports from UPMC and University of Nebraska for details related to the genomic biomarkers and statistical work.

2. **KEYWORDS:** *Pancreatic cysts, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, serous cystadenoma, pancreatic cancer, pancreatic adenocarcinoma, early detection, radiomics, cyst fluid, genomics.*

3. **ACCOMPLISHMENTS:**

   - **What were the major goals of the project?**

     - Specific Aim 1: To assess if the combination of radiomic and genomic biomarkers are superior in performance than each assay alone in the detection of mucinous cysts and advanced neoplasia

     - Specific Aim 2: To evaluate the role of radiomic and genomic biomarkers to prognosticate mucinous cysts

     - Specific Aim 3: To determine if advancements in quantitative imaging analysis and in next generation sequencing can further enhance the performance of radiomic and genomic biomarkers

   - **What was accomplished under these goals?**

     - ***Major activities****:* In the first 12 months of this grant, imaging studies from 187 subjects at UPMC were sent to MD Anderson. Dr. Koay's group has performed blinded radiomic analysis of imaging from 127 subjects. In our SOW, these analyses are relevant to Major Task 1 and Major Task 2 of Specific Aim 1, as well as Major Task 3 of Specific Aim 2. Relevant to Major Task 3 of Specific Aim 3, we have developed workflows to apply enhancement pattern mapping to CT scans of patients with IPMNs and have performed preliminary analyses of a test set from MD Anderson.

     - ***Specific objectives****:* It should be noted that no Milestone were proposed to be completed in Year 1. The following tasks were proposed in the first 12 months of this grant in the SOW:

Award Task: To provide time for approval from the Army Human Resource Protection Office (HRPO). (Months 1-3) : Accomplished

Major Task 1 is to evaluate the performance of individual and combined radiomic and genomic biomarkers in the identification of mucinous cysts in the pancreas. (Months 1-18) 75% completed (3 of 4 subtasks)

Major Task 2 is to evaluate individual and combined performance of radiomic and genomic biomarkers in the detection of advanced neoplasia within a mucinous cyst. (Months 3-20) 40% completed

Major Task 3 is to perform radiomic evaluation of prognosis for patients undergoing surveillance for pancreatic cysts. (Months 10-26) 10% completed

Major Task 7: Pilot study of 50 patients with MRI scans and cyst fluid for biomarker assessment (Months 3-18) 60% completed

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- ***Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)****:*

A major portion of the first year's tasks were focused on the identification and collection of scans and cyst fluids for Major Tasks 1, 2 and 3.

Aim 1: cases detailed below consist of 126 subjects with CT only, 28 subjects with MRI only, and 33 subjects with both CT and MRI sent
Major Task 1
115/115 (100%) subjects with mucinous surgical cysts
38/115 (33%) subjects with non-mucinous surgical cysts

Major Task 2
35/115 (30%) subjects with mucinous advanced neoplasia (degenerated into invasive cancer or HGD)
114/150 (76%) subjects with mucinous LGD

Aim 2: Training set- 95 identified of 400 clinical or surgical mucinous cysts

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Radiomics

Dr. Koay's group developed a deep learning algorithm to automatically segment the pancreas on CT scans, which is our first step in developing an approach to automated cyst detection within the pancreas volume. This automated pancreas segmentation algorithm provides a 3D DICOM RT structure as a segmentation volume as an output. We trained this algorithm on a dataset of 100 manually segmented pancreas organs from CT scans from our available datasets and had a radiologist review all of the manual segmentations for accuracy. We used four deep learning models in this investigation: attention Unet (attUnet), 2D DeepLabV3+, 3D patch-based BasicUnet from MONAI, and 2-step Unet from RaySearch Laboratories (RSLab). The deep learning model performance was compared to manual segmentation using the Dice similarity coefficient (DSC). The median (min-max) DSC for 0.78 (0.16-0.88), 0.80 (0.44-0.89), 0.80 (0.00-0.88), 0.82 (0.34-0.88), 0.82 (0.59-0.89), for the attUnet, DeepLabV3+, RSLab, MONAI, and MV models. We are currently refining this model to improve performance and will evaluate performance using a majority vote approach of all the models combined. As we receive additional

scans from UPMC in a blinded fashion, we will apply this pancreas autosegmentation model to the scans. In parallel, we are developing a similar deep learning model for automated cyst detection within the volume that our pancreas autosegmentation model creates. We plan to expand the study on additional cases available to us. An example of the pancreas and cyst autodetection is shown in the Figure below.

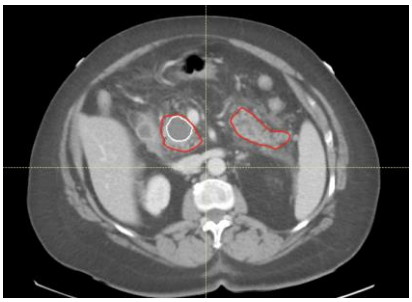

Figure: Autosegmentation of the pancreas (red outline) and an IPMN within the pancreas (white outline). We trained deep learning algorithms a set of 100 manually segmented pancreas and cyst cases from our dataset and measured performance using the Dice Similarity Coefficient.

Genomics

Dr. Singhi at UPMC has collected genomic data for those subjects identified in Task 1 and is in the process of sending this data to Dr. Lynette Smith at UNMC for analysis. The genomic data as outlined within our proposal includes targeted next-generation sequencing (NGS) of single nucleotide variants, small insertions and deletions, copy number analysis and loss of heterozygosity using single nucleotide polymorphisms. The panel for testing includes 22 genes of tumor suppressor genes and oncogenes with a depth of coverage of 1000x and allele frequency that is validated at 0.5%. Genomic alterations are identified based on AMP/CAP/ASCO guidelines using a tiered approach to include Tier 1 and Tier 2 mutations.

- Other achievements: Related to Major Task 3, we have applied enhancement pattern (EPM) mapping to CT scans of patients with IPMNs. We are analyzing these in the context of differentiating patients who have high grade dysplasia and low grade dysplasia based on the EPM signals. We anticipate completing a multi-institutional study of using EPM for identifying the malignant potential (or not) of IPMNs in the coming year.

Major findings are limited at this time since the formal analysis of the genomic data and radiomic data alone and combined proposed for specific aims 1 and 2 is planned for Year 2 of the grant.

- **What opportunities for training and professional development has the project provided?**

  - Julia Douglas is a research assistant I in the Koay Lab at MD Anderson. She did not have radiomic experience prior to starting this project and has learned multiple new skills during the course of this first year, including image registration, coding, segmentation, quality review, and texture analyses that are relevant to the project. She has also learned how a major grant project is conducted by participating in the monthly team meetings that we have with the participating sites. She will be submitting an abstract related to the work in the coming months.

- **How were the results disseminated to communities of interest?**

  - We described some of the pancreas autosegmentation results at PancreasFest 2022 in Pittsburgh in July 2022. We will submit an abstract on the autosegmentation models to a major national meeting in the coming months once we have additional data. A manuscript will subsequently follow.

- **What do you plan to do during the next reporting period to accomplish the goals?**

    - Dr. Koay at MD Anderson will continue to refine our autosegmentation algorithms with collaborators and his team, produce radiomic data for analysis by our statistical team relevant to Aims 1, 2, and 3, and write at least one abstract and one manuscript describing our findings.

    - Dr. Brand at UPMC is in the process of obtaining additional scans from the following outside institutions: Stanford, West Virginia University and UT Southwestern, to complete our goal numbers of scans and cysts. (See section 5 for additional discussion).

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

    - The impact of this project will be on the clinical management of pancreatic cysts and the early detection of pancreatic cancer. On one level, our autosegmentation approach will provide a detection tool that can be used by the community to analyse pancreatic cysts on CT scans using tools that use DICOM data as inputs. Our approach of using radiomic and next-generation imaging tools like enhancement pattern mapping may point to quantitative ways to assess mucinous cysts in the pancreas and prognosticate them.

- **What was the impact on other disciplines?**

    - The field of computer vision and machine learning may borrow some of our approaches to autosegmentation and apply them to other organ systems.

- **What was the impact on technology transfer?**

    - Nothing to Report.

- **What was the impact on society beyond science and technology?**

    - Nothing to Report

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**: Nothing to report

- **Actual or anticipated problems or delays and actions or plans to resolve them:**

    We had anticipated the possibility that UPMC would not be able to provide all of the scans with associated cyst fluid available for genomic analysis at the time of grant submission. As expected, the two groups that have been difficult to identify are subjects with non-mucinous cysts and subjects with advanced neoplasia who underwent surgical resection. As mentioned earlier, we are approaching Stanford, West Virginia University and UT Southwestern to contribute scans to the project. We are requesting subject with both mucinous and non-mucinous cysts as well as those surgically resected individuals with advanced neoplasia and low-grade dysplasia. If number of subjects with surgically resected non-mucinous cysts still remains low, we plan on including a subset of patients who have imaging and cyst fluid with classic presentation of benign cyst and thus did not undergo surgical resection.

- **Changes that had a significant impact on expenditures:** Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:** Nothing to Report

- **Significant changes in use or care of human subjects:** Nothing to Report
- **Significant changes in use or care of vertebrate animals:** Nothing to Report
- **Significant changes in use of biohazards and/or select agents:** Nothing to Report

6. **PRODUCTS**

- **Publications, conference papers, and presentations:** Nothing to Report

  - **Journal publications.** Nothing to Report
  - **Books or other non-periodical, one-time publications.** Nothing to Report
  - **Other publications, conference papers, and presentations.** Nothing to report

- **Website(s) or other Internet site(s):** Nothing to Report

- **Technologies or techniques***:* Our deep learning algorithms for pancreas autosegmentation will be shared through our publications. We have provided these models through Github in the past.

- **Inventions, patent applications, and/or licenses**
  Nothing to Report.

- **Other Products**
  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	*Randall Brand No Change except for funding*
Project Role:	*PI at UPMC*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	Oversees the complete project including selection of the cases and controls and blinding process.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Aatur Singhi No Change except for funding*
Project Role:	*Co-PI at UPMC*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	Oversees the molecular cyst fluid analysis including interpretation of the results
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Anil Dasyam No Change*
Project Role:	*Co-I*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0,3
Contribution to Project:	Oversees the de-identification of imaging studies and serves as a radiology resource for the project.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Suzanne Burdin No Change*
Project Role:	*Radiology honest broker*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	
Contribution to Project:	Serves as the honest broker who de-identifies imaging scans to be shared with MD Anderson.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Nancy Abubaker No Change*
Project Role:	*Research Technician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.4
Contribution to Project:	Assists in ongoing cyst fluid collection and pulling of samples for cyst fluid analysis for molecular studies.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Christine DeCapite Worthington No Change*
Project Role:	*Clinical research coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Assists in the identification of subjects for the study who have both cyst fluid and imaging tests.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Saurabh Divakaran*
Project Role:	*Research coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	She is a molecular technician within Dr. Singhi's laboratory and is responsible for day-to-day molecular testing.
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Lynette Smith No Change*
Project Role:	*Co-PI at UNMC*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-0836-9932*
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Smith is preparing for data analysis and algorithm development. Dr. Smith is researching variable selection methods to ensure optimal model development without overfitting.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Jihyun Ma No Change*
Project Role:	*Statistician*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-4761-9607*
Nearest person month worked:	1.8
Contribution to Project:	*Jihyun Ma will be assisting Dr. Smith with data analysis as data transfers are completed.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Eugene Koay No Change*
Project Role:	*PI at MD Anderson*
Researcher Identifier (e.g. ORCID ID):	*ORCID ID: 0000-0001-7675-3461*
Nearest person month worked:	1.2
Contribution to Project:	*Dr. Koay has coordinated the radiomic efforts for the project. He has performed analyses on the images, directed the coding of the pancreas and cyst autosegmentation algorithms, and directed the work of Julia Douglas (see below). He is responsible for all the radiomic work related to this grant.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Julia Douglas No Change*
Project Role:	*Research assistant at MD Anderson*
Researcher Identifier (e.g. ORCID ID):	0000-0001-9322-2769
Nearest person month worked:	3.36
Contribution to Project:	*Julia has worked with the UPMC team to organize and transfer the images from UPMC to MD Anderson. She works in Dr. Koay's lab and is responsible for reviewing the images for quality and type of scan (CT or MRI). She is performing manual segmentation of the images for deep learning development and radiomic analyses. She participates in all of the DOD grant meetings for the team and meets with Dr. Koay weekly to ensure progress for the study.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Gabriela Fuentes No Change*
Project Role:	*Research Data Coordinator at MD Anderson*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.78
Contribution to Project:	*Gabriela has helped to organize the DOD imaging databases and do initial processing of the images with Julia Douglas. Gabriela meets with Dr. Koay on a weekly basis to ensure progress on the study.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*David Fuentes No Change*
Project Role:	*Collaborator - Associate Professor in Cancer Systems Imaging at MD Anderson*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.34
Contribution to Project:	*Dr. Fuentes has helped develop the workflows for automated image processing of large imaging databases like the DOD study.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

Name:	*Millicent Roach No Change*
Project Role:	*Research assistant at MD Anderson*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.40
Contribution to Project:	*Millicent has helped with manual segmentation of images in this project. She has also helped with downloading the images from UPMC and processing them with Julia. Millicent meets with Dr. Koay on a weekly basis to ensure progress with the grant.*
Funding Support:	*None relevant to this project beyond the current DOD award.*

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - For Drs. Brand and Singhi EDRN funded U01 CA200466 and U01 CA152653 have closed this past year
- **What other organizations were involved as partners?**
  - Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**
   - **COLLABORATIVE AWARDS:** We are submitting a combined report from UPMC and MD Anderson as part of this DOD award.
9. **APPENDICES:** Nothing to Report